JACC: CARDIOVASCULAR INTERVENTIONS VOL. 5, NO. 9, 2012

ISSN 1936-8798/$36.00

PUBLISHED BY ELSEVIER INC.

http://dx.doi.org/10.1016/j.jcin.2012.05.010

Association Between Periprocedural Bleeding and Long-Term Outcomes Following Percutaneous Coronary Intervention in Older Patients

Sunil V. Rao, MD,* David Dai, PhD, MS,* Sumeet Subherwal, MD, MBA,* William S. Weintraub, MD,† Ralph S. Brindis, MD, MPH,‡ John C. Messenger, MD,§ Renato D. Lopes, MD, PhD,* Eric D. Peterson, MD, MPH*

Durham, North Carolina; Newark, Delaware; San Francisco, California; and Denver, Colorado

Objectives The authors sought to describe the association between post-procedural bleeding and long-term recurrent bleeding, major adverse cardiac events (MACE), and mortality among older patients undergoing percutaneous coronary intervention (PCI).

Background Bleeding complications after PCI are associated with an increased risk for acute morbidity and long-term mortality, but the association of these bleeding complications with other events is unknown.

Methods Patients entered into the National Cardiovascular Data Registry (NCDR) CathPCI Registry (n = 461,311; 946 sites) from January 2004 to December 2008 were linked with claims from the Centers for Medicare & Medicaid Services and grouped according to in-hospital post-PCI bleeding. The association between post-PCI bleeding and 1-, 12-, and 30-month readmission for bleeding, MACE, and all-cause mortality was examined with Cox regression that included patient and procedural characteristics using no bleeding as the reference.

Results Overall, 3.1% (n = 14,107) of patients experienced post-PCI bleeding. Patients who bled were older, more often female, had more medical comorbidities, less often received bivalirudin, and more often underwent PCI via the femoral approach. After adjustment, bleeding after the index procedure was significantly associated with readmission for bleeding (adjusted hazard ratios [95% confidence interval]: 1 month, 1.54 [1.42 to 1.67]; 12 months, 1.52 [1.40 to 1.66]; 30 months, 1.29 [1.11 to 1.50]), MACE (1 month, 1.11 [1.07 to 1.15]; 12 months, 1.17 [1.13 to 1.21]; 30 months, 1.12 [1.06 to 1.19]) and all-cause mortality (1 month, 1.32 [1.26 to 1.38]; 12 months, 1.33 [1.27 to 1.40]); 30 months, 1.22 [1.15 to 1.30]).

Conclusions Post-PCI bleeding complications are associated with an increased risk for short- and long-term recurrent bleeding, MACE, and all-cause mortality. These data underscore the prognostic importance of periprocedural bleeding and the need for identifying strategies to reduce long-term bleeding risk among patients undergoing PCI. (J Am Coll Cardiol Intv 2012;5:958–65) © 2012 by the American College of Cardiology Foundation

From the *Duke Clinical Research Institute, Durham, North Carolina; †Christiana Health Care System, Newark, Delaware; ‡San Francisco Kaiser Permanente Hospital, San Francisco, California; and the §Denver Veterans Affairs Medical Center, Denver, Colorado. This analysis was supported by the American College of Cardiology and The Medicines Company, Parsippany, New Jersey. The Medicines Company did not have input into the design of the study nor in the preparation of the paper. Dr. Rao has received research funding from Ikaria and Sanofi-Aventis (<$10,000), and consulting fees from The Medicines Company, Terumo, and Zoll (<$10,000). Dr. Lopes has received research grant support from Bristol-Myers Squibb (>$10,000). Dr. Peterson has received research grant support from Eli Lilly and Johnson & Johnson (>$10,000). All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Manuscript received March 6, 2012; revised manuscript received May 7, 2012, accepted May 12, 2012.

Bleeding complications that occur after percutaneous coronary intervention (PCI) are associated with an increased risk for morbidity and all-cause mortality (1). Mechanisms underlying this association are unclear but likely include cessation of evidence-based medical therapy (2); blood transfusion (1); the effect of comorbidities among patients who develop bleeding (3); or the effect of bleeding itself when bleeding is intracranial or retroperitoneal. Despite the lack of clarity on the pathophysiological explanations, the adverse prognostic impact of bleeding has been noted in the outpatient setting as well, with up to 11% of patients discontinuing at least 1 antiplatelet agent due to so-called "nuisance" bleeding (4). Identification of patients at high bleeding risk has been proposed as a way to selectively implement "bleeding avoidance strategies" (5,6).

Most studies examining the prognostic impact of bleeding have examined outcomes associated with either in-hospital (5) or out-of-hospital bleeding (7), but not both. In addition, these studies have primarily examined mortality or ischemic events as the outcome; few studies have assessed the relationship between acute bleeding and both recurrent bleeding and ischemic events that occur over the long term. It remains unclear whether patients who develop hemorrhagic complications after PCI continue to be at risk for bleeding complications long after the procedure. This is an important issue, given the need for prolonged antithrombotic therapy for secondary prevention (8,9) and the differential bleeding profiles of various evidence-based discharge antithrombotic therapies. Accordingly, we used a large contemporary registry of patients undergoing PCI to examine the association between post-PCI bleeding and long-term outcomes, including readmission for bleeding events.

Methods

Patient population. The National Cardiovascular Data Registry (NCDR) CathPCI Registry, which is cosponsored by the American College of Cardiology and the Society for Cardiovascular Angiography and Interventions, has been previously described (10). The CathPCI Registry collects data on patient and hospital characteristics, clinical presentation, treatments, and outcomes for PCI procedures from over 1,000 sites across the United States. Data are entered into NCDR-certified software at participating institutions, and exported in a standard format to the American College of Cardiology. There is a comprehensive data quality program, including both data quality report specifications for data capture and transmission, and an auditing program. A committee of the American College of Cardiology prospectively defined the variables, which are available at the NCDR website.

For the purpose of this analysis, we included the first PCI procedure performed in any individual patient during a qualifying hospitalization between January 2004 and December 2008. The dataset comprised 1,725,600 admissions from 967 sites. Patients who died during hospitalization (n = 22,029) and patients for whom bleeding data were missing (n = 61; 1 site) were excluded. The study was approved by the institutional review board of Duke University Medical Center, which determined that the study met the definition of research not requiring informed consent.

Linkage to claims data. The CathPCI Registry only contains data on in-hospital outcomes. In order to determine the association between in-hospital bleeding complications and longer-term outcomes, we linked CathPCI Registry patients over the age of 65 years with the Medicare 100% Part A claims file (11). Percutaneous coronary intervention procedure codes (International Classification of Diseases-Ninth Revision-Clinical Modification [ICD-9-CM], 00.66, 36.0x, 37.22, 37.23, and 88.5x, except 88.59) were used to identify index procedures in the Medicare files, which were then linked to the CathPCI Registry using indirect identifiers (non-unique fields that when used in combination may identify unique hospitalizations). Linking rules used a hierarchy of evidence approach such that rules with the greatest specificity were applied first. Once a match was achieved for a patient, no further rules were applied. The linking rules contained combinations of information denoting the index PCI procedure site, patient date of birth or age, admission, discharge date, and sex. If a single CathPCI Registry record matched with multiple Medicare records using the same rules, then no linking occurred. Unidentified longitudinal profiles were obtained with up to 30 months of patient follow-up. Sites that did not match to Medicare records and patients whose index PCI procedure did not occur during a period of fee-for-service enrollment were excluded. This study included all Medicare-linked patients ≥65 years of age undergoing PCI who were enrolled in the CathPCI Registry from January 1, 2004, to December 31, 2008.

Abbreviations and Acronyms

MACE = major adverse cardiac event(s)

MI = myocardial infarction

PCI = percutaneous coronary intervention

STEMI = ST-segment elevation myocardial infarction

Endpoints and definitions. The outcomes for this analysis were readmission for bleeding, major adverse cardiac events (MACE) (defined as the composite of death, myocardial infarction [MI], or revascularization), and all-cause mortality. Outcomes were evaluated at 1 month, 12 months, and 30 months. We also examined the use of evidence-based medications at hospital discharge (defined as the prescription of aspirin, clopidogrel, beta-blockers, statins, and angiotensin-converting enzyme inhibitors) between patients who bled versus those who did not, and compared length of stay between the 2 groups.

To identify patients who experienced post-PCI bleeding, we used the definition of bleeding in the CathPCI Registry (i.e., access site bleeding, retroperitoneal bleeding, gastrointestinal bleeding, genitourinary bleeding, or other). All bleeding events in the registry are further defined as requiring transfusion and/or prolonging the hospital stay, and/or causing a drop in hemoglobin >3.0 g/dl. Hematomas >10 cm for femoral access or >2 cm for radial access qualify as access site bleeding. We also grouped patients according to access site bleeding, defined as overt access site bleeding or retroperitoneal bleeding, and non-access site bleeding, defined as all other bleeding events. Readmissions for bleeding were identified from claims data using the ICD-9-CM diagnosis codes: Bleeding 430 to 432, 578.X, 719.1X, 423.0, 599.7, 626.2, 626.6, 626.8, 627.0, 627.1, 786.3, 784.7, or 459.0. Myocardial infarction and revascularization events that occurred during follow-up were obtained from claims data using the ICD-9-CM diagnosis code 410.X1 (MI) and ICD-9-CM procedure codes 36.00, 36.06, 36.07, 36.09, and 36.10 to 36.19 (revascularization). Only revascularizations occurring after discharge from the index hospital stay were included for the MACE endpoint. All-cause mortality was obtained from the claims data file.

Statistical analysis. Patients were grouped according to whether they experienced a post-procedure bleeding event. For descriptive analyses, baseline characteristics and treatment strategies were compared between patients who bled versus those who did not. Continuous variables are presented as medians with interquartile percentiles, and categorical variables are presented as percentages. Differences between patient groups were compared using chi-square tests for categorical variables and the Wilcoxon rank sum test for continuous variables, respectively.

Estimates of the event rates for clinical endpoints at 1 month, 12 months, and 30 months post-intervention were determined on the basis of weights that were functions of Kaplan-Meier censoring estimates (12). The cumulative incidence rates for time-to-event clinical outcomes were estimated by using Gray's method (13). Both the unadjusted and adjusted hazard ratios were estimated for in-hospital bleeding versus no bleeding along with a 95% confidence interval on the basis of the sandwich-estimated standard errors. The adjusted analysis include the variables adopted in the CathPCI Registry in-hospital all-cause mortality model as covariates, which consist of age, body mass index, glomerular filtration rate, ST-segment elevation myocardial infarction (STEMI), cardiogenic shock at admission, medical history (i.e., congestive heart failure, valvular surgery, cerebrovascular disease, peripheral vascular disease, chronic lung disease, diabetes, dialysis, PCI), highest-risk lesion characteristics (segment category), New York Heart Association functional class, pre-procedure intra-aortic balloon pump, coronary lesion ≥50%, and PCI status (14). In addition, we used landmark analysis to determine the 30-month component of the in-hospital bleeding effect after excluding events between 30 days and 12 months. The entire analysis was repeated to examine the relationship

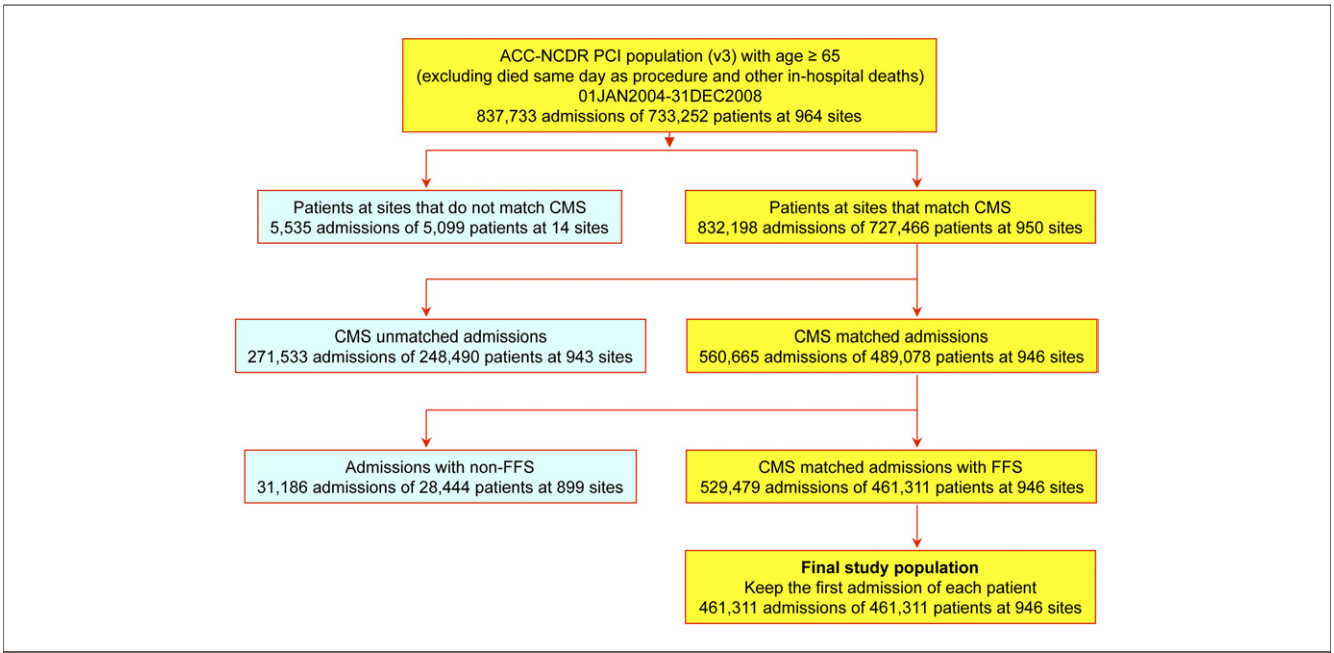

Figure 1. Study Sample Selection Flow Diagram

Displays initial study population through the final study population, exclusions included. ACC = American College of Cardiology; CMS = Centers for Medicare & Medicaid Services; FFS = fee for service; NCDR = National Cardiovascular Data Registry; PCI = percutaneous coronary intervention.

between access site and non-access site bleeding and the outcomes, using no bleeding as the reference. A p value <0.05 was considered significant for all tests. The Duke Clinical Research Institute performed all statistical analyses using SAS software (version 9.2, SAS Institute, Cary, North Carolina).

Results

Patient sample and baseline characteristics. The final study sample included 837,733 patients from 964 sites. After matching to Medicare claims, the analysis dataset included 461,311 patients from 946 sites (Fig. 1), 14,107 (3.1%) of whom experienced bleeding. Among patients who bled, 48.6% had access site bleeding. The rate of blood transfusion was 5.5%. Baseline characteristics of the patients who did and did not develop bleeding are listed in Table 1. Patients who bled were older and more often female. They also had a lower body mass index, and more often had comorbidities, such as chronic kidney disease, peripheral arterial disease, cerebrovascular disease, and congestive heart failure. By contrast, there was a similar prevalence of diabetes mellitus and hypertension between the 2 groups.

With respect to presenting symptoms, patients who bled more often presented with acute coronary syndrome (either non-STEMI or STEMI) rather than stable angina. In addition, there was a higher proportion of urgent, emergent,

Table 1. Baseline Characteristics of Patients Who Did and Did Not Develop In-Hospital Bleeding

Characteristic	Overall (n = 461,311)	Bleeding (n = 14,107)	No Bleeding (n = 447,204)	p Value
Demographics				
Age, yrs	74.0 (69.0–80.0)	76.0 (71.0–81.0)	74.0 (69.0–80.0)	<0.001
Female	42.0	57.5	42.5	<0.001
BMI, kg/m^2	27.7 (24.7–31.5)	27.3 (24.0–31.3)	27.7 (24.7–31.5)	<0.001
Medical comorbidities				
Diabetes mellitus	33.5	33.7	33.5	0.593
Hypertension	82.0	82.5	82.0	0.145
Peripheral arterial disease	15.3	17.9	15.2	<0.001
Chronic kidney disease	7.0	10.1	6.9	<0.001
Prior CHF	72.7	81.1	72.5	<0.001
Prior PCI	29.6	20.6	29.9	<0.001
Prior CABG	23.1	17.4	23.3	<0.001
Procedure characteristics				
Procedure indication				
Stable angina/atypical chest pain/asymptomatic	37.3	23.0	37.6	<0.001
Non–ST-segment ACS	51.3	50.5	51.4	<0.001
STEMI	11.5	26.5	11.0	<0.001
Procedure status				
Elective	48.4	29.1	49.0	<0.001
Urgent	38.5	40.5	38.5	<0.001
Emergency	12.9	29.8	12.4	<0.001
Medications*				
Aspirin	90.2	91.2	90.1	<0.001
Clopidogrel	76.5	73.6	76.6	<0.0001
Unfractionated heparin	53.8	69.4	53.3	<0.001
LMWH	16.7	20.6	16.6	<0.001
Bivalirudin	40.8	27.5	41.2	<0.001
Any GP IIb/IIIa	38.2	61.3	37.4	<0.001
Vascular access site				
Radial	1.2	0.8	1.2	<0.001
Femoral	97.9	97.9	97.9	0.863
Brachial	0.4	0.7	0.4	<0.001

Values are median (interquartile range) or percentages. *Includes medications given at the time of admission through the catheterization lab visit.

ACS = acute coronary syndrome; BMI = body mass index; CABG = coronary artery bypass grafting; CHF = congestive heart failure; GP = glycoprotein; LMWH = low-molecular-weight heparin; PCI = percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction.

Table 2. Unadjusted Rates of Evidence-Based Medications at Discharge and Differences in Hospital Length of Stay Between Groups

Outcome	In-Hospital Bleeding (n = 14,107)	No In-Hospital Bleeding (n = 447,204)	p Value
Discharge medications			
Aspirin	94.6	95.6	<0.001
Clopidogrel	92.2	95.7	<0.001
Beta-blocker	85.8	80.1	<0.001
Statin	81.0	82.2	<0.001
ACE inhibitor	52.5	48.5	<0.001
Median post-procedure LOS, days	6.0 (4.0–9.0)	2.0 (2.0–3.0)	<0.001

Values are % or median (interquartile range).
ACE = angiotensin-converting enzyme; LOS = length of stay.

and salvage procedures among patients who developed bleeding. In-hospital medical therapies and procedural approaches also differed between the groups: the use of unfractionated heparin, low-molecular-weight heparins, and glycoprotein IIb/IIIa inhibitors was higher among patients who bled. In contrast, the use of bivalirudin, pre-PCI clopidogrel, and radial access was lower.

Table 2 displays the use of evidence-based medications at the time of hospital discharge among patients who bled versus those who did not. The use of antiplatelet agents and other secondary prevention medications was significantly lower among patients who bled, with the exception of beta-blockers and angiotensin-converting enzyme inhibitors, which were prescribed more often to patients who developed a bleeding complication. The hospital length of stay was significantly longer for patients who developed bleeding compared with those who did not (median length of stay: 6.0 vs. 2.0 days, $p < 0.0001$).

Outcomes. The unadjusted rates of the outcomes are listed in Table 3. The rates of readmission for bleeding at 1 month, 12 months, and 30 months were significantly higher among patients who experienced in-hospital bleeding. Similarly, unadjusted MACE and all-cause mortality rates at 1 month, 12 months, and 30 months were also significantly higher among patients who developed in-hospital bleeding. Figures 2A to 2C show the Kaplan-Meier rates of the endpoints.

Adjusted results. Figure 3 displays the association between post-procedure bleeding and readmission for bleeding, all-cause mortality, and MACE after adjustment for potential confounders. Compared with patients who did not bleed, the risk for all 3 outcomes was significantly higher at all 3 time points for patients who experienced in-hospital bleeding. At the 30-month time point, the risk for recurrent bleeding and all-cause mortality attenuated slightly, but was still significantly higher for patients who bled compared with patients who did not bleed. The risk for MACE remained stable over time and was significantly higher for patients who bled compared with those who did not bleed. The relationships between access site and non-access site bleeding and outcomes are shown in Online Table 1 in the Online Appendix.

Table 3. Rates of the Primary and Secondary Clinical Endpoints Between Groups

Outcome	In-Hospital Bleeding (n = 14,107)	No In-Hospital Bleeding (n = 447,204)	p Value
Readmission for bleeding			
1 month	0.9 (0.7–1.0)	0.3 (0.3–0.4)	<0.001
12 months	3.9 (3.5–4.3)	1.9 (1.9–2.0)	<0.001
30 months	5.9 (5.2–6.6)	3.4 (3.3–3.5)	<0.001
MACE*			
1 month	6.7 (6.2–7.2)	5.7 (5.6–5.8)	<0.001
12 months	30.6 (29.5–31.7)	24.1 (23.9–24.3)	<0.001
30 months	51.4 (49.4–53.3)	43.5 (43.2–43.9)	<0.001
All-cause mortality			
1 month	2.3 (2.1–2.6)	1.0 (1.0–1.1)	<0.001
12 months	13.7 (13.1–14.3)	6.9 (6.8–6.9)	<0.001
30 months	24.1 (23.2–25.0)	14.2 (14.1–14.3)	<0.001

Values are % (95% confidence intervals). *Death, MI, revascularization.
MACE = major adverse cardiac events; MI = myocardial infarction.

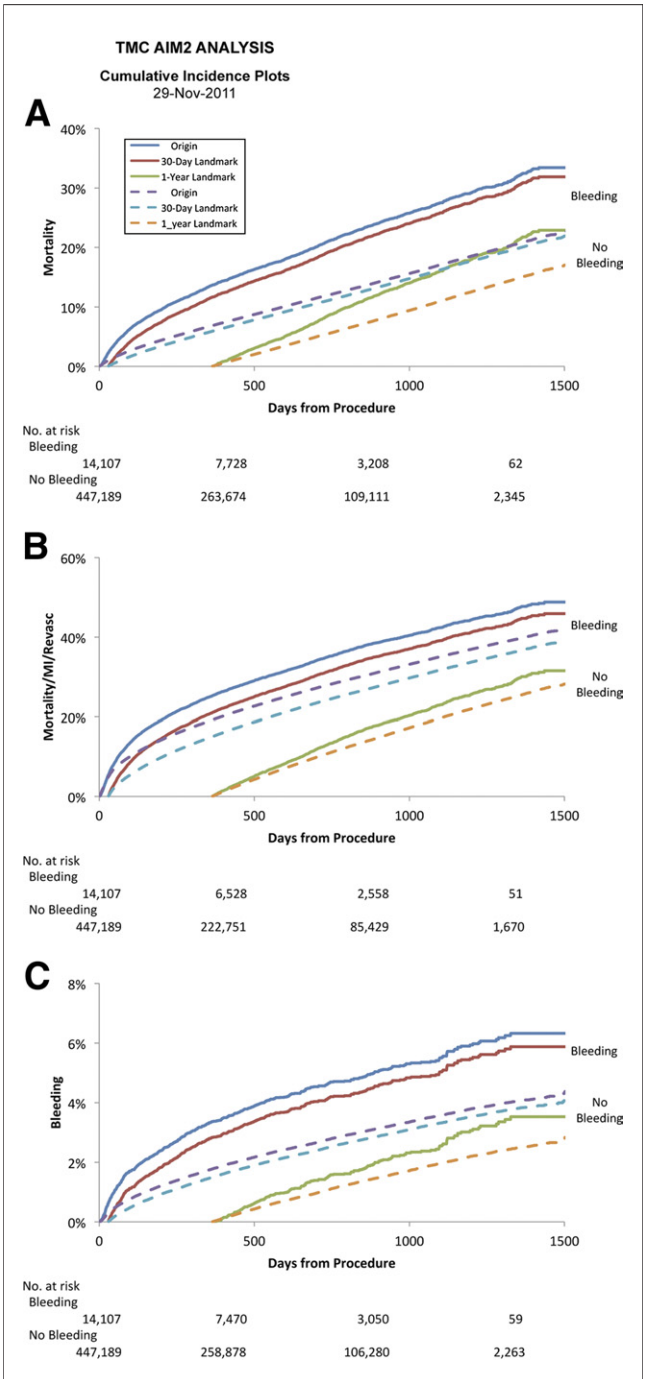

Figure 2. Kaplan-Meier Rates

(A) Kaplan-Meier rates of readmission for bleeding between patients who developed periprocedural bleeding and those who did not; **(B)** Kaplan-Meier rate of major adverse cardiac events (MACE) between patients who developed periprocedural bleeding and those who did not; **(C)** Kaplan-Meier rates of all-cause mortality between patients who developed periprocedural bleeding and those who did not.

Discussion

In the largest analysis of its kind involving over 400,000 older patients, we found that post-PCI bleeding is associated with an increased risk for future bleeding complications, MACE, and all-cause mortality. Although the association between bleeding and long-term mortality among patients undergoing PCI has been previously described, the present study has 2 important new findings: 1) the association between post-procedure bleeding and outcomes extends out to 30 months; and 2) patients who develop post-procedure bleeding are prone to recurrent bleeding events over the long term. Thus, post-procedure bleeding identifies a patient population that is at risk for poor net adverse clinical events.

The association between bleeding and ischemic outcomes has been previously described. Kinnaird et al. (15) examined the association between Thrombolysis In Myocardial Infarction (TIMI) major and minor bleeding, as well as blood transfusion, and in-hospital and 1-year mortality among 10,974 unselected patients undergoing PCI and found that TIMI major bleeding was independently associated with in-hospital, but not 1-year, mortality. By contrast, blood transfusion was associated with increased mortality at both time points. Subsequent studies using different bleeding definitions have found that bleeding and transfusion are associated with short- and long-term mortality, MACE, target vessel revascularization, stent thrombosis, and stroke (16–18). Yet none of these studies examined the risk of recurrent bleeding. Our study, which is larger than all previous studies combined, confirms the findings of prior studies, but also extends them by demonstrating that bleeding identifies a group that is at high risk for continued bleeding events in the outpatient setting.

Putative mechanisms that underlie the association between hemorrhagic complications and ischemic outcomes include cessation of evidence-based therapy (2), the negative effects of blood transfusion (1,19), a direct effect of the bleeding itself on oxygen delivery or, rarely, exsanguination, and potentially an increased propensity for thrombosis, due to bleeding. Studies have explored these mechanisms in the inpatient setting, but little is known about the mechanisms that apply in the outpatient setting. With respect to recurrent bleeding events, it is likely that patients who are vulnerable to bleeding from acute antithrombotic therapy and invasive procedures are also susceptible to bleeding with chronic antithrombotic therapies. In the present study, patients who developed a bleeding complication were older, more often had a lower body weight, and more often had comorbidities, such as chronic kidney disease, diabetes, and peripheral arterial disease. Many of these risk factors are associated with bleeding during chronic therapy with dual antiplatelet therapy (7). This consistency in characteristics associated with bleeding across care settings underscores the

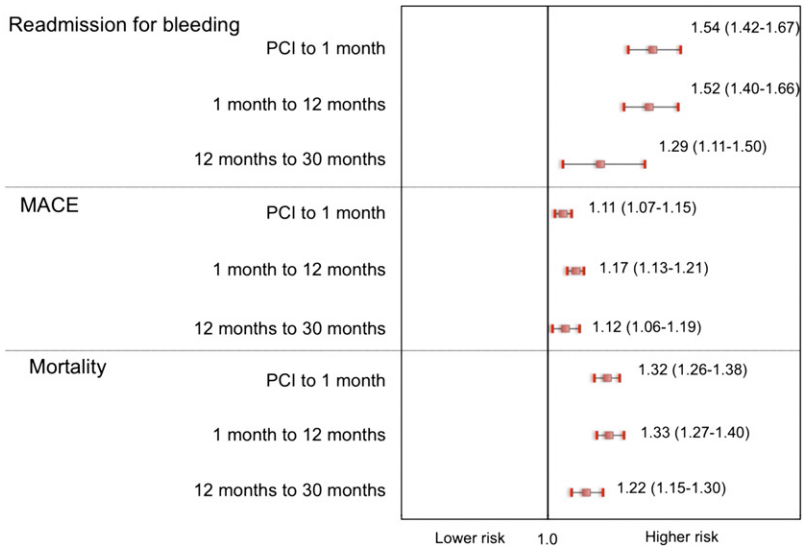

Figure 3. Adjusted Association Between In-Hospital Bleeding, Recurrent Bleeding, MACE, and All-Cause Mortality

Hazard ratios for outcomes are shown with landmarks at 30 days and 1 year. All-cause mortality adjusted for age, chronic lung disease, EF, NYHA functional class, diabetes, prior CHF, BMI, dialysis, GFR, PAD, CVD, urgent PCI, shock, emergent PCI, sex, primary PCI, lesion risk, pre-PCI IABP, salvage PCI, prior valve disease, race, STEMI, TIMI flow, and stent thrombosis. MACE adjusted for diabetes, EF, dialysis, lesion risk, chronic lung disease, prior CHF, BMI, PAD, CVD, GFR, NYHA functional class, emergent PCI, pre-PCI IABP, shock, TIMI flow grade, urgent PCI, age, STEMI, primary PCI, salvage PCI, race, prior valve disease, and stent thrombosis. BMI = body mass index; CHF = congestive heart failure; CVD = cerebrovascular disease; EF = ejection fraction; GFR = glomerular filtration rate; IABP = intra-aortic balloon pump; MACE = major adverse cardiac event; NYHA = New York Heart Association; PAD = peripheral artery disease; PCI = percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction; TIMI = Thrombolysis In Myocardial Infarction.

importance of monitoring these high-risk patients for both ischemic and bleeding complications from the time of PCI through long-term outpatient follow-up.

In the contemporary era of PCI, several strategies exist to reduce the risk of periprocedural bleeding (20,21). Clinical trials have shown that some of these strategies are associated with reduced all-cause mortality in specific settings (22,23). For example, the use of bivalirudin is associated with a significant reduction in both access site and non-access site bleeding (24), and is associated with reduced short- and long-term mortality among patients undergoing primary PCI (25). Similarly, the use of radial access is also associated with a significant reduction in access site bleeding and vascular complications, but is less frequently used in patients at higher risk for such complications (26). Although these strategies reduce the risk for in-hospital bleeding, neither is applicable in the outpatient setting. There are few proven approaches associated with reduced bleeding risk during chronic treatment for coronary artery disease. Reduction in aspirin dosing may be associated with lower bleeding rates during long-term therapy (27), but not within 30 days of an acute coronary syndrome episode (28). Another strategy is to avoid the use of potent thienopyridines in patients at high risk for bleeding, such as older patients, those with prior stroke or transient ischemic attack, and those with body weight <60 kg (29). Ticagrelor, a non-thienopyridine P2Y12 antagonist, has been shown to reduce ischemic events, including stent thrombosis, over the long term without an increase in major bleeding (30), and this agent may be preferred in patients at risk for bleeding.

Study limitations. First, we relied on linkage to administrative data to obtain long-term outcomes. This necessarily limited our population to patients who were age 65 years or older. In addition, nonmortal events, such as bleeding, revascularization, or MI were obtained from Medicare data, which may lead to missing events due to coding bias. We also could not completely account for differences in severity across events defined by the ICD-9 codes. Second, we did not have data on patient frailty, which may account, in part, for the outcomes. Third, although it is possible that some of the bleeding events that occurred during follow-up may have been associated with repeat percutaneous procedures, we minimized this possibility by limiting the bleeding outcomes to hospitalization specifically for a bleeding event. Finally, unmeasured confounders may be present. To minimize this, we used a robust statistical adjustment; however, causality cannot be inferred from our findings.

Conclusions

Among older patients, post-PCI bleeding complications are associated with an increased risk for short- and long-term

readmission for bleeding, MACE, and all-cause mortality. These data underscore the prognostic importance of bleeding and the need for identifying strategies to reduce both procedural and long-term bleeding risk among patients undergoing PCI.

Reprint requests and correspondence: Dr. Sunil V. Rao, Duke Clinical Research Institute, Durham Veterans Affairs Medical Center, 508 Fulton Street (111A), Durham, North Carolina 27705. E-mail: sunil.rao@duke.edu.

REFERENCES

1. Doyle BJ, Rihal CS, Gastineau DA, Holmes DR Jr. Bleeding, blood transfusion, and increased mortality after percutaneous coronary intervention: implications for contemporary practice. J Am Coll Cardiol 2009;53:2019–27.
2. Wang TY, Xiao L, Alexander KP, et al. Antiplatelet therapy use after discharge among acute myocardial infarction patients with in-hospital bleeding. Circulation 2008;118:2139–45.
3. Spencer FA, Moscucci M, Granger CB, et al. Does comorbidity account for the excess mortality in patients with major bleeding in acute myocardial infarction? Circulation 2007;116:2793–801.
4. Roy P, Bonello L, Torguson R, et al. Impact of "nuisance" bleeding on clopidogrel compliance in patients undergoing intracoronary drug-eluting stent implantation. Am J Cardiol 2008;102:1614–7.
5. Mehta SK, Frutkin AD, Lindsey JB, et al. Bleeding in patients undergoing percutaneous coronary intervention: the development of a clinical risk algorithm from the national cardiovascular data registry. Circ Cardiovasc Interv 2009;2:222–9.
6. Marso SP, Amin AP, House JA, et al. Association between use of bleeding avoidance strategies and risk of periprocedural bleeding among patients undergoing percutaneous coronary intervention. JAMA 2010;303:2156–64.
7. Ducrocq G, Wallace JS, Baron G, et al. Risk score to predict serious bleeding in stable outpatients with or at risk of atherothrombosis. Eur Heart J 2010;31:1257–65.
8. Anderson JL, Adams CD, Antman EM, et al. ACC/AHA 2007 guidelines for the management of patients with unstable angina/non ST-elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 2002 Guidelines for the Management of Patients With Unstable Angina/Non ST-Elevation Myocardial Infarction). J Am Coll Cardiol 2007;50:e1–157.
9. Mega JL, Braunwald E, Wiviott SD, et al., for the ATLAS ACS 2–TIMI 51 Investigators. Rivaroxaban in patients with a recent acute coronary syndrome. N Engl J Med 2012;366:9–19.
10. Brindis RG, Fitzgerald S, Anderson HV, Shaw RE, Weintraub WS, Williams JF. The American College of Cardiology-National Cardiovascular Data Registry (ACC-NCDR): building a national clinical data repository. J Am Coll Cardiol 2001;37:2240–5.
11. Douglas PS, Brennan JM, Anstrom KJ, et al. Clinical effectiveness of coronary stents in elderly persons: results from 262,700 Medicare patients in the American College of Cardiology National Cardiovascular Data Registry. J Am Coll Cardiol 2009;53:1629–41.
12. Bang H, Tsiatis AA. Median regression with censored cost data. Biometrics 2002;58:643–9.
13. Gray RJ. A class of K-sample tests for comparing the cumulative incidence of a competing risk. Ann Statist 1988;16:1141–54.
14. Peterson ED, Dai D, DeLong ER, et al. Contemporary mortality risk prediction for percutaneous coronary intervention: results from 588,398 procedures in the National Cardiovascular Data Registry. J Am Coll Cardiol 2010;55:1923–32.
15. Kinnaird TD, Stabile E, Mintz GS, et al. Incidence, predictors, and prognostic implications of bleeding and blood transfusion following percutaneous coronary interventions. Am J Cardiol 2003;92:930–5.
16. Manoukian SV, Feit F, Mehran R, et al. Impact of major bleeding on 30-day mortality and clinical outcomes in patients with acute coronary syndromes: an analysis from the ACUITY trial. J Am Coll Cardiol 2007;49:1362–8.
17. Yatskar L, Selzer F, Feit F, et al. Access site hematoma requiring blood transfusion predicts mortality in patients undergoing percutaneous coronary intervention: data from the National Heart, Lung, and Blood Institute Dynamic Registry. Catheter Cardiovasc Interv 2007;69:961–6.
18. Suh JW, Mehran R, Claessen BE, et al. Impact of in-hospital major bleeding on late clinical outcomes after primary percutaneous coronary intervention in acute myocardial infarction the HORIZONS-AMI (Harmonizing Outcomes With Revascularization and Stents in Acute Myocardial Infarction) trial. J Am Coll Cardiol 2011;58:1750–6.
19. Rao SV, Eikelboom JA, Granger CB, Harrington RA, Califf RM, Bassand JP. Bleeding and blood transfusion issues in patients with non-ST-segment elevation acute coronary syndromes. Eur Heart J 2007;28:1193–204.
20. Rao SV, Ohman EM. Anticoagulant therapy for percutaneous coronary intervention. Circ Cardiovasc Interv 2010;3:80–8.
21. Rao SV, Ou FS, Wang TY, et al. Trends in the prevalence and outcomes of radial and femoral approaches to percutaneous coronary intervention: a report from the National Cardiovascular Data Registry. J Am Coll Cardiol Intv 2008;1:379–86.
22. Yusuf S, Mehta SR, Chrolavicius SR, et al. Comparison of fondaparinux and enoxaparin in acute coronary syndromes. N Engl J Med 2006;354:1464–76.
23. Stone GW, Witzenbichler B, Guagliumi G, et al. Bivalirudin during primary PCI in acute myocardial infarction. N Engl J Med 2008;358:2218–30.
24. Verheugt FW, Steinhubl SR, Hamon M, et al. Incidence, prognostic impact, and influence of antithrombotic therapy on access and nonaccess site bleeding in percutaneous coronary intervention. J Am Coll Cardiol Intv 2011;4:191–7.
25. Mehran R, Lansky AJ, Witzenbichler B, et al. Bivalirudin in patients undergoing primary angioplasty for acute myocardial infarction (HORIZONS-AMI): 1-year results of a randomised controlled trial. Lancet 2009;374:1149–59.
26. Rao SV, Ou FS, Wang TY, et al. Trends in the prevalence and outcomes of radial and femoral approaches to percutaneous coronary intervention: a report from the National Cardiovascular Data Registry. J Am Coll Cardiol Intv 2008;1:379–86.
27. Campbell CL, Smyth S, Montalescot G, Steinhubl SR. Aspirin dose for the prevention of cardiovascular disease: a systematic review. JAMA 2007;297:2018–24.
28. Mehta SR, Bassand JP, Chrolavicius S, et al. Dose comparisons of clopidogrel and aspirin in acute coronary syndromes. N Engl J Med 2010;363:930–42.
29. Wiviott SD, Braunwald E, McCabe CH, et al. Prasugrel versus clopidogrel in patients with acute coronary syndromes. N Engl J Med 2007;357:2001–15.
30. Wallentin L, Becker RC, Budaj A, et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. N Engl J Med 2009;361:1045–57.

Key Words: elderly patients ■ percutaneous coronary intervention ■ periprocedural bleeding.

APPENDIX

For a supplementary table, please see the online version of this paper.